Synthesis of Poly-*N*-(thiazol-2-yl)methacrylamide: Characterization, Complexation, and Bioactivity

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ABSTRACT: Cu(II) complexes with *N*-(thiazol-2-yl)methacrylamide (NTM) and its polymer PNTM have been synthesized. The ligands (NTM and PNTM) and their Cu(II) complexes have been characterized by FTIR and ^{1}H-NMR. EDX was performed to know the elemental composition and X-ray powder diffractometry (XRD) analysis was applied to detect the crystallinity of the complexes. The morphology of these complexes was investigated with scanning electron microscopy (SEM) and proves that the monomer complexes have a strongly crystalline structure compared with the polymer complexes, which show that it is only weakly crystalline. These results from SEM are in agreement with results obtained from XRD. Thermal properties of the ligands and their complexes have been studied by thermogravimetric analysis and differential scanning calorimetry. The activity of the ligands and their complexes has been screened against *S. aureus, E. coli, Pseudomonas*, and *Candida albicans*. The synthesized compounds have shown good affinity as antibacterial and antifungal agents, which increased on complexation with Cu(II) ion. The results of these studies show the Cu(II) complexes to be more thermal stable as compared with NTM and PNTM. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 117: 3679–3686, 2010

Key words: thiazole compound; polymerization; complexation; biological activity

INTRODUCTION

The synthesis of new polymer ligands has great practical and theoretical interest.[1,2] This interest originates from applications in analytical chemistry[3] and industry.[4] Beside the removal of toxic metal ions through the use of chelating polymers could be of great important in environmental applications.[5] The coordination behavior of metals has been investigated.[6–8]

Heterocycles are one of the most fascinating targets for synthetic organic chemists because of their potentially high biological activities.[9–12] Many synthetic derivatives of thiazole show remarkable antimicrobial activities.[9–13] For example, nocathiacins are densely functionalized cyclic thiazolyl peptide natural products with potent *in vitro* and *in vivo* antibacterial activity against a variety of gram-positive bacteria, including a number of multiple drug-resistant strains.[13] Thus, synthesis of polymer containing heterocyclic moiety is considered as one of our goals. In addition, the use of transition metal centers and multidentate ligands for directing the assembly of complex structures has been developed into one of the most widely used strategies for organizing molecular building blocks into supramolecular arrays in the last decade.[14] An important goal in constructing coordination polymers is design functional molecular materials, which have potential applications as catalytic, conductive, luminescent, magnetic, spin-transition, nonlinear optical, and/or nanoporous materials.[14–18] This article is considered as continuation for our work in this area,[19,20] where we have aimed to prepare a new monomer and transferred into the corresponding polymer. Using of the prepared polymer in biological study and waste treatment through study of its ability to complex with different metal ion is considered one of our targets.

EXPERIMENTAL

Materials

Methacryloyl chloride and 2-aminothiazole (Aldrich) were used as received. All metal salts and solvents were reagent grade and used without further purification.

Synthesis of monomer *N*-(thiazol-2-yl) methacrylamide

Ice cold solution of methacryloyl chloride (0.01 mol) in acetone (30 mL) was added dropwise to cold

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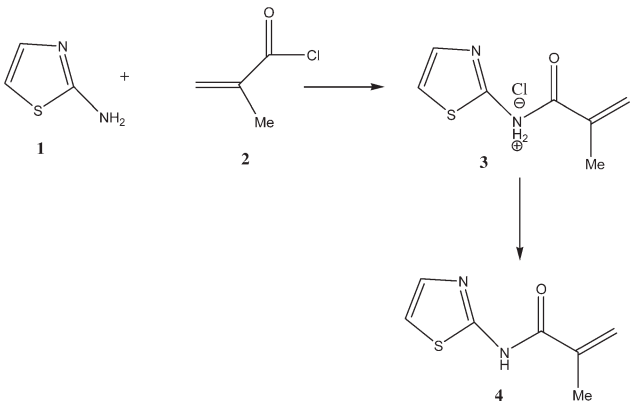


Scheme 1 Synthesis of monomer *N*-(thiazol-2-yl)methacrylamide (NTM).

solution of 2-aminothiazole (0.01 mol) in acetone (30 mL). The reaction temperature kept in range from 0 to 5°C for 2 h after addition. The reaction mixture was neutralized with saturated solution of ammonium hydrogen carbonate to give *N*-(thiazol-2-yl)methacrylamide (NTM). The solid product was collected by filtration, washed with cold water (2 × 100 mL), and crystallized from ethanol to give NTM with 90% yield and m.p. 190°C. Elemental analysis found to be C = 49.98%, H = 4.79%, N = 16.65%, and S = 19.06% calculated: C = 50.01%, H = 4.82%, N = 16.60%, and S = 19.30%. Scheme 1 shows the synthesis of NTM.

Polymerization (PNTM)

The free radical polymerization of vinyl monomer NTM (0.01 mol) was carried out in dimethylformamide (30 mL) using azobisisobutyronitrile (AIBN) as (0.01% mol) initiator at 75°C. The polymeric solution poured into mixture of ethanol/water (1 : 1), the precipitated polymer **(**PNTM) filtered, and washed with ethanol. The polymer purified by refluxing in ethanol and finally dried in the vacuum at 40°C for 48 hr.

Synthesis of complexes

Two different methods have been applied to prepare complexes.

Method A

The synthesized polymer PNTM (0.01 mol), was refluxed with a metal salt (0.01 mol), copper (II) chloride ($CuCl_2$), or copper (II) acetate (CuAc) 0.01 mol, in DMF (50 mL) for 5 h. The reaction mixture was left overnight and then filtered, washed, and dried in vacuum at 60°C until constant weight was obtained.

Method B

Equivalent amount of monomer (0.01 mol) and the corresponding metal salt (0.01 mol) dissolved in DMF (50 mL). AIBN (0.01 mol %) was added to the mixture as initiator. The reaction was carried out in a water thermostat adjusted to 75°C for 24 h. The mixture was poured into a large excess of ethanol/water (1 : 1) mixture to precipitate the complex. The obtained complexes were purified by reprecipitation once or twice and then dried in a vacuum oven at 60°C until constant weight was obtained.

Procedure of biological tests

Ten milligram of the tested compounds was uniformly distributed in a well of 6 mm diameter made by a borer in the seeded agar medium. After that bacterial test plates were incubated at 37°C for 24 h and fungal test plates were incubated at 25°C for 48 h. The activities were expressed as inhibition zones (mm, diameter, as clear areas).[21–23]

Characterization

Elemental analysis was performed at Analab, on LECO CHNS – 932. Infrared (IR) spectra were taken in the range 400–4000 cm^{-1} using Perkin Elmer FTIR spectrometer 2000. ^{1}H-NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument with TMS as internal reference. The thermogravimetric analysis (TGA) on the samples was performed using the Schimadzu TG analyzer by heating the sample (~ 15 mg) from ambient to 800°C at a heating rate of 10°C/min with air flow rate of 50 mL/min. X-ray powder diffractometry (XRD) was carried out at ambient temperature, using a D5000 Siemens diffractometer equipped with a source of Ni-filtered CuKα radiation (λ = 1.5406 Å). The diffractometer was operated at 40 kV and 30 mA, and the data were acquired stepwise in the 2θ range 5–80° with a step size of 0.02°, a step time of 15 s, and a divergence slit of 1°, using an on line microcomputer. The morphology of the test materials has been studied using a JSM-630 Jeol scanning electron microscope operated at 20 kV.

Energy dispersive spectroscopy (EDS) chemical area mapping for test materials was done with LINK's exl II energy dispersive spectrometer (Oxford Instrument, UK) attached to scanning electron microscope to detect metal ion in the polymeric complexes.

Electron spin resonance (ESR) measurements were carried out at room temperature with a Bruker spectrometer, model ECS 106 in the x-band range (9.4 GHz). The *g*-values were estimated using a variant-standard ″stong-pitch″ with $g = 2.0028$. The powder

of test material was placed in the sample tubes. Stretching direction of the sample was either parallel or perpendicular to the axis of the magnetic field.

RESULTS AND DISCUSSION

Synthesis of monomer

The target monomer NTM (**4**) was synthesized upon treating cold solution of 2-aminothiazole (**1**) with methacryloyl chloride (**2**) to give a pale yellow precipitate of the hydrochloride form (**3**). Treatment of the obtained salt with aqueous solution of ammonium hydrogen carbonate furnishes a free base monomer NTM (**4**) in excellent yield, 90% (*cf.* Scheme 1).

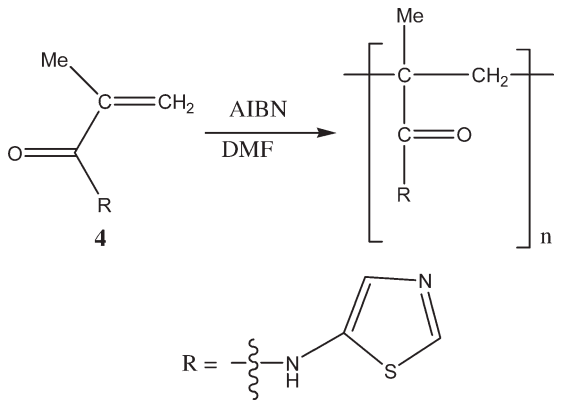
Synthesis of polymer

Radical solution polymerization of the prepared monomers NTM was carried out in DMF solvent in the presence of AIBN at 75°C with continuous steam of nitrogen gas was bubbled through the reaction medium. Polymer could be precipitated via addition of ethanol/water mixture (1 : 1). The same reaction product with very little difference in the yield could be obtained without bubbling of nitrogen gas during polymerization process. The polymers were collected by filtration and purified by refluxing in ethanol for 3 h (*cf.* Scheme 2).

Identification of monomer and polymer

Infrared spectra of the prepared monomer and polymer

The monomer and polymer structures were characterized by FTIR and ^{1}H-NMR. Figure 1(A) shows characteristic bands representing chemical bonds in the NTM molecule, including the band at 1629 cm^{-1} because of overtone symmetric stretching of —CH=CH$_2$. The sharp band appearing at



Scheme 2 Synthesis of poly-*N*-(thiazol-2-yl)methacrylamide (NTM).

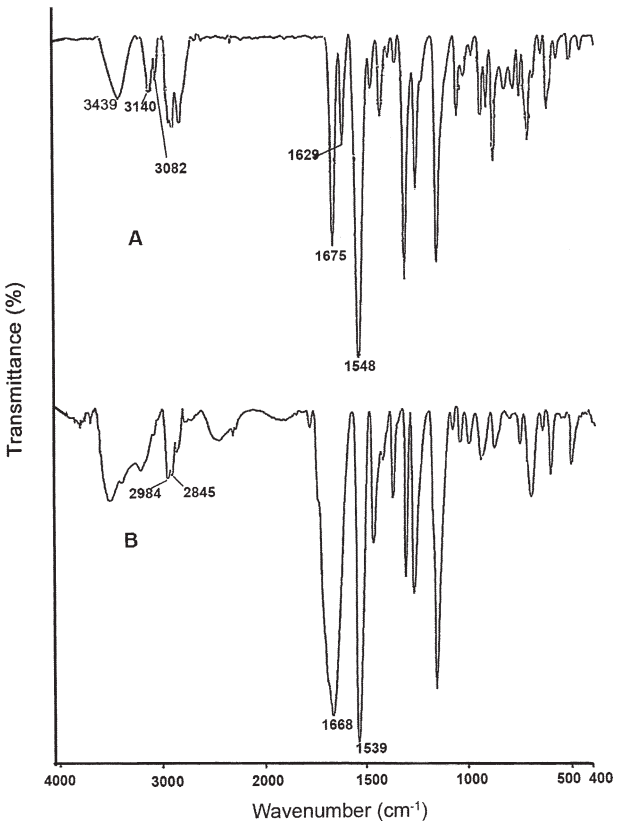


Figure 1 FTIR spectra for monomer NTM (A), polymer PNTM (B).

1548 cm^{-1} can be attributed to thiazole ring. The absorption bands appearing at 3082 and 3140 cm^{-1} due to =CH$_2$ and band at 3439 cm^{-1} can be attributed to N—H. Also stretching sharp band at 1675 cm^{-1} is due to amide carbonyl. The formation of PNTM is confirmed in the FTIR spectrum of the polymer. Figure 1(B) shows disappearance of —CH=CH$_2$ band at 1629 cm^{-1} and =CH$_2$ bands at 3082 and 3140 cm^{-1} are not observed, whereas a broad absorption band appeared at 2984 and 2845 may be due to CH$_2$ and CH$_3$ aliphatic chain stretching vibration. The broad band around 714 cm^{-1} may be due to $(CH_2)_n$ [where $n = 4$ or more] revealing the completion of polymerization. In addition a broad amide carbonyl band at 1668 cm^{-1} confirms formation of the polymer.

^{1}H-NMR spectrum of the prepared monomer and polymer

The extent of polymerization has been investigated by ^{1}H-NMR spectroscopy as shown Figure 2. The signals characteristic for the monomer [Fig. 2(A)] disappear and the corresponding broad bands for polymer [Fig. 2(B)] show up. The proton signal of the N—H group at δ 12.17 ppm of monomer decreases in intensity, meanwhile a broad band appears at δ 12.55 ppm in polymer spectrum. At the

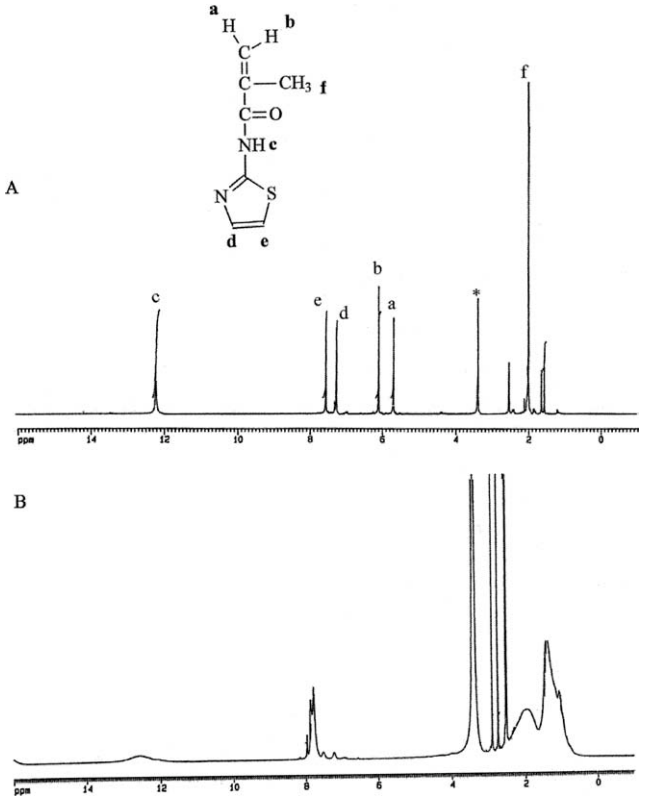


Figure 2 ^{1}H-NMR spectra for monomer NTM (A), polymer PNTM (B).

same time, the doublet of ethylenic proton signals at δ 6.06 and 5.66 ppm in monomer spectrum disappeared and two new peaks appeared at δ 2.89 and 2.73 ppm in the polymer spectrum due to methylene protons. Methyl protons appeared at δ 1.97 ppm decreases in intensity and a broad band appears in the same region in the polymer spectrum confirming polymeric structure. In addition, the expanding of peaks in case of monomer show a doublet of doublet for thiazole protons at δ 7.52 and 7.23 ppm with *J* values equal to 4 Hz. Although in case of the polymer, a little shift is observed with interface of doublet at δ 7.95 and 7.52 ppm.

Mass spectra of the prepared monomers

Mass spectrum of the monomer NTM shows molecular ion peak at 168 (M^+, 45 %) in Figure 3, which in agreement with the molecular formula $C_7H_8N_2SO$.

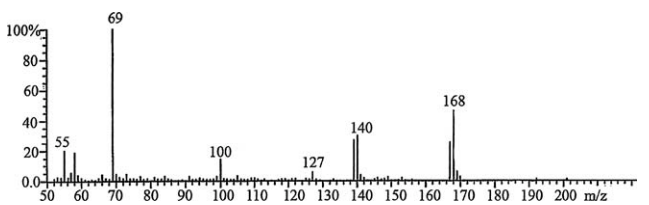
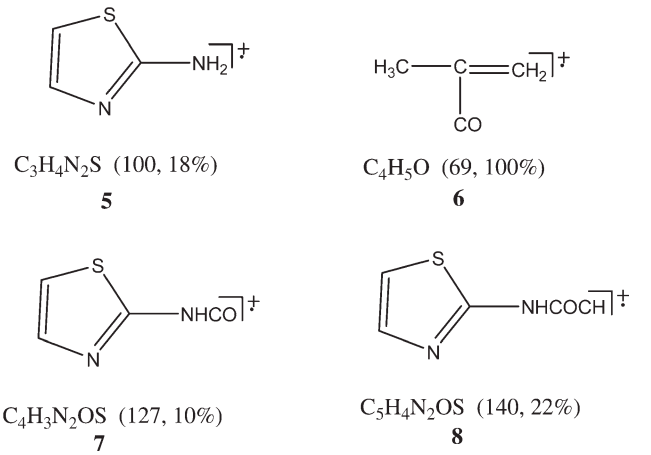


Figure 3 The mass spectrum of monomer NTM.



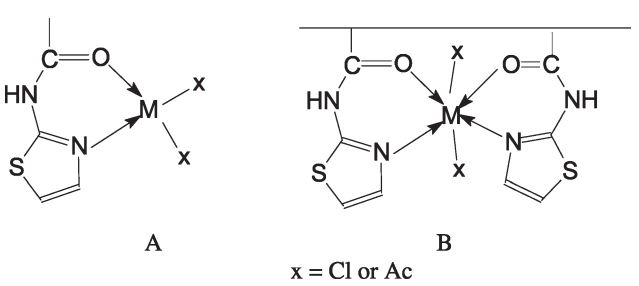
Scheme 3 The mass spectrum shows main fragments of monomer NTM.

The mass spectrum shows main fragments at *m/z* 100 (18%), 69 (100%), 127 (10%), and 140 (22%), which are corresponding to fragments **5, 6, 7,** and **8** in Scheme 3.

Characterization of NTM and PNTM complexes

Radical polymerization of monomer in the presence of copper salts (hydrated $CuCl_2$ or Cu-Ac) and AIBN at 75°C in DMF solvent resulted in the formation of Cu-monomer complexes NTM-$CuCl_2$ and NTM-CuAc. However, metallopolymer complexes PNTM-$CuCl_2$ and PNTM-CuAc produced by direct interaction between polymer PNTM and Cu(II) ion in DMF at 150°C. Figure 4 shows IR spectra of (A) NTM-$CuCl_2$ and (B) PNTM-$CuCl_2$. In comparison, obvious changes were observed between the IR of the two complexes. The spectrum of NTM-$CuCl_2$ displays band 1629 cm^{-1} due to —CH=CH_2, which is absent in PNTM-$CuCl_2$. This indicates that Cu(II) inhibit the polymerization reaction. The IR spectrum of copper containing monomer, the band due to $\nu_{C=O}$ is slightly shifted from 1675 to 1686, whereas ν_{N-H} remained unchanged upon complexation.

In the IR spectrum metallopolymer (PNTM-$CuCl_2$), the band at 1539 cm^{-1} because of the thiazole ring in the pure polymer is shifted to 1542 cm^{-1}.



Scheme 4 Suggested structures of the metal complexes with NTM and PNTM.

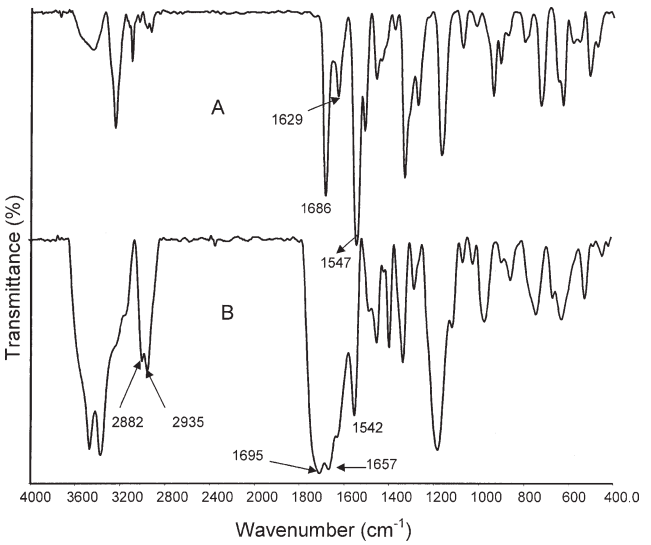


Figure 4 FTIR spectra for $CuCl_2$ complexes NTM-$CuCl_2$ (A), PNTM-$CuCl_2$ (B).

The PNTM-$CuCl_2$ complex exhibits characteristic IR bands at 1657 cm^{-1}, which could be assigned to ν(C═N). The band due to $\nu_{C=O}$ is shifted from 1668 cm^{-1} to a broad band at 1695 cm^{-1}. The bands at 2882 and 2935 cm^{-1}, Figure 4(B), were attributed to the stretching vibration of the aliphatic C—H. Figure 5 shows IR spectrum of (A) NTM-CuAc and (B) PNTM-CuAc. The spectrum of PNTM-CuAc did not exhibit bands at 3111 due to $=CH_2$, whereas it exists in NTM-CuAc spectrum confirming that the former is a polymer and the latter is a monomer. The band due to $\nu_{C=O}$ is slightly shifted from 1675 in the pure monomer to 1679 cm^{-1} in NTM-CuAc and from 1668 cm^{-1} in the pure polymer to 1657 cm^{-1} in PNTM-CuAc spectrum. The band at 1548 cm^{-1} due to thiazole in NTM is shifted to 1519 cm^{-1} in NTM-CuAc and from 1539 in pure polymer to 1544 cm^{-1} in PNTMT-CuAc spectrum. Furthermore, the acetate anion exhibits two bands at 1393 and 1614 cm^{-1} with $\Delta\nu = 221$ cm^{-1} in case of NTM-CuAc characteristic of monodentate acetate group. In case of the complex prepared by refluxing, PNTM-CuAc, the two bands appeared at 1389 and 1443 cm^{-1} with $\Delta\nu = 54$ cm^{-1} suggesting its bidentate in nature. This suggests that the metal ion chelate with the nitrogen of the thiazole ring and carbonyl oxygen to form stable six-membered ring in PNTM-Cu complexes. Accordingly, the structures A and B in Scheme 4, could be assumed for isolated complexes.

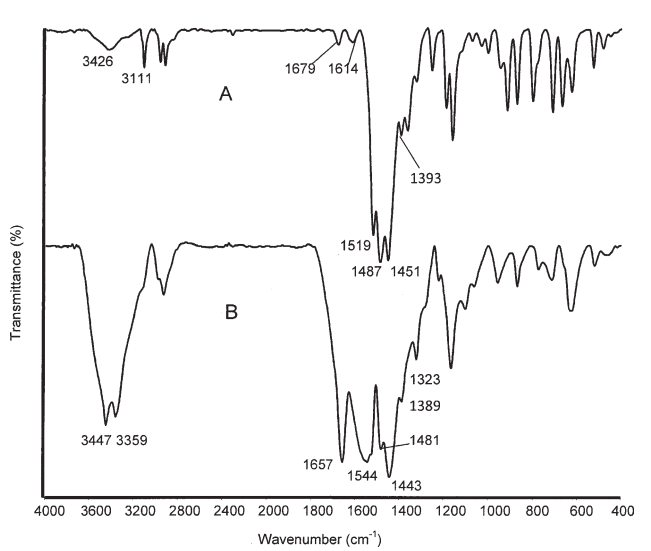


Figure 5 FTIR spectra for CuAc complexes NTM-CuAc (A), PNTM-CuAc (B).

ESR of the prepared metallopolymer complexes

The room temperature X-band ESR spectrum of the crystalline NTM-$CuCl_2$ [Fig. 6(A)] shows an axial-type with $g_{\|} = 2.24$, $g_{\perp} = 2.059$, and $g_{av} = 2.12$. The data suggests the population of $dx^2 - y^2$ in the ground state, which is consistent with a tetragonally distorted structure. The value of $G = 4.07$ indicate a $dx^2 - y^2$ ground state with a slightly distortion. However, the spectrum of complex resulted from the reaction of $Cu(CH_3COO)_2{\cdot}2H_2O$ with NTM [Fig. 6(C)] exhibits a quaisotropic shape with g value of 2.088. The shape of the metallopolymer complexes obtained from the reaction of $CuCl_2{\cdot}2H_2O$ [Fig. 6(B)] and $Cu(CH_3COO)_2{\cdot}2H_2O$ [Fig. 6(D)] with PNTM are of axial type with $g_{\|} = 2.51$, 2.47 and $g_{\perp} = 2.12$, 2.11, respectively. The trend $g_{\|} > g_{\perp}$ suggests the presence of unpaired electrons in $dx^2{-}y^2$ orbital of copper. The extent of the exchange interaction in solid state $G = 4.25$, 4.27 indicates that the population $dx^2 - y^2$ in the ground state with a slightly distortion.

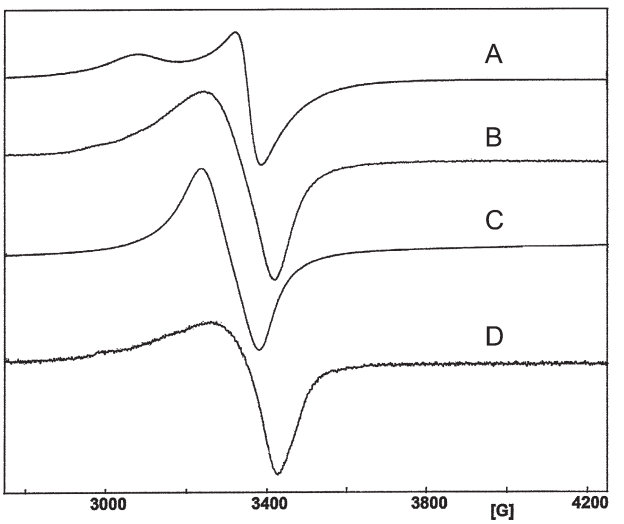


Figure 6 ESR spectra for $CuCl_2$ complexes: (A) NTM-$CuCl_2$, (B) PNTM-$CuCl_2$, (C) NTM-CuAc, and (D) PNTM-CuAc.

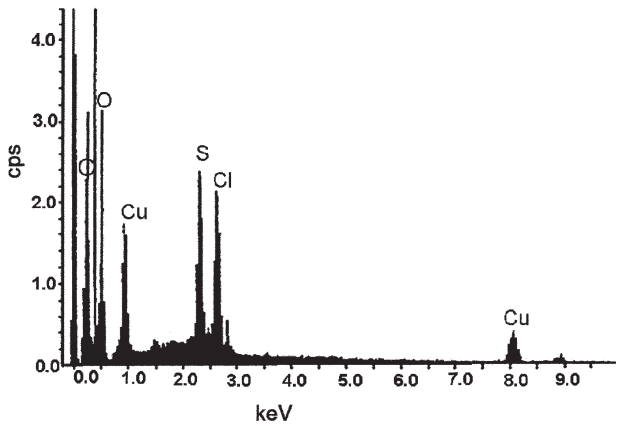


Figure 7 EDS of PNTM-$CuCl_2$ complex.

Morphology, EDS and XRD of metallomonomer and metallopolymer complexes

The energy dispersion composition (EDX) of NTM-$CuCl_2$, NTM-CuAc, PNTM-$CuCl_2$, and PNTM-CuAc complexes was performed to know the elemental composition of these complexes. Figure 7 displays the EDX spectrum for PNTM-$CuCl_2$. It can be seen that Cu^{2+} ion taken up by polymer and a similar spectrum is obtained for all complexes.

The synthesized NTM-$CuCl_2$, PNTM-$CuCl_2$, NTM-CuAc, and PNTM-CuAc complexes were characterized using scanning electron microscopy (SEM) to know the morphologies of these complexes.

The SEM micrograph obtained for complexes are displayed in Figure 8. Monomer complexes show large well-developed crystals. Shape of NTM-CuAc particles are in the form of aggregated needle-like particles or thread-like gathered in a rod form, whereas the shape of NTM-$CuCl_2$ particles in the form of radiating rose-like in one or more direction from a central point. In contrast, in polymer complexes, the particles are small and amorphous. PNTM-CuAc particles are seen to be small irregular granular beads and PNTM-$CuCl_2$ particles are small and granular in shape. These results are in agreement with the results obtained by XRD. XRD suggests (Fig. 9) that the monomer complexes have a strongly crystalline structure compared with the polymer complexes, which shows that it is only weakly crystalline.

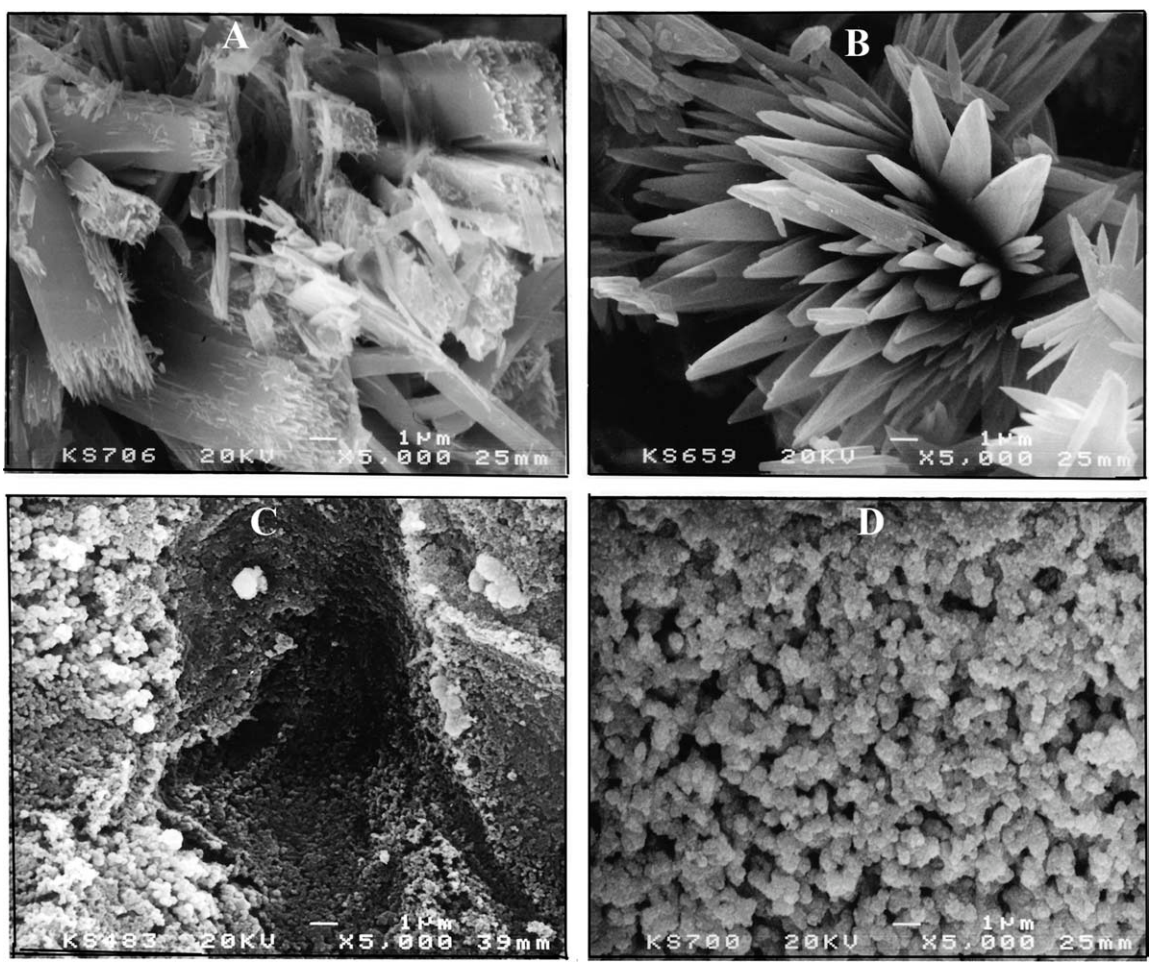


Figure 8 Scanning electron micrographs for complexes: NTM-CuAc (A), PNTM-$CuCl_2$ (B), PNTM-CuAc (C), and PNTM-$CuCl_2$ (D).

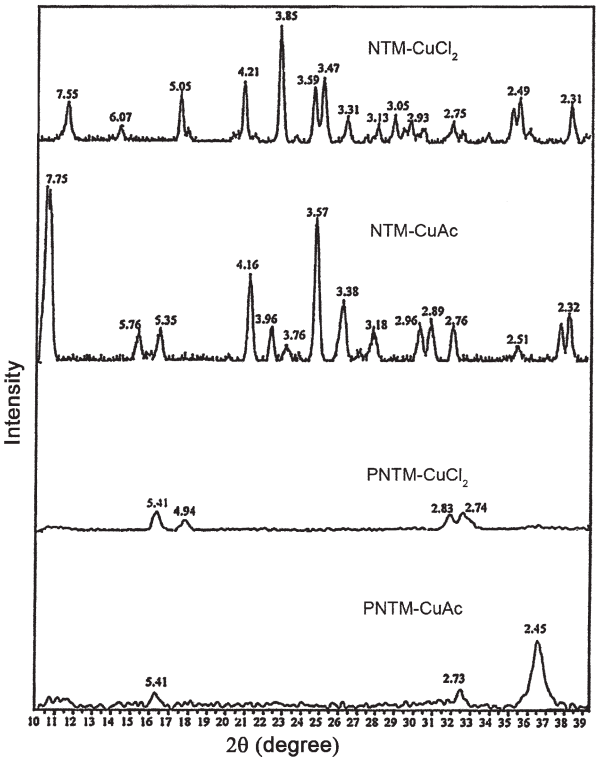


Figure 9 XRD for complexes: NTM-CuAc, NTM-$CuCl_2$, PNTM-CuAc, and PNTM-$CuCl_2$.

TGA and DTA of the polymer and metallopolymer complexes

TGA and DTA analysis are the easy methods to study the thermal degradation behavior in which loss of a sample is measured continuously, whereas the temperature is changed at a constant rate. TG and DTG of the monomer NTM and polymer PNTM are given in Figure 10. Table II illustrates the thermal decomposition temperatures of NTM, PNTM, and their Cu complexes. The TG curve of monomer NTM show the initial weight loss at temperature 240°C followed by another weight loss at 534°C. For the case of PNTM, the first weight loss is around 236°C, which is less than 4%. Maximum loss is found to be at temperature 433°C. The weight loss

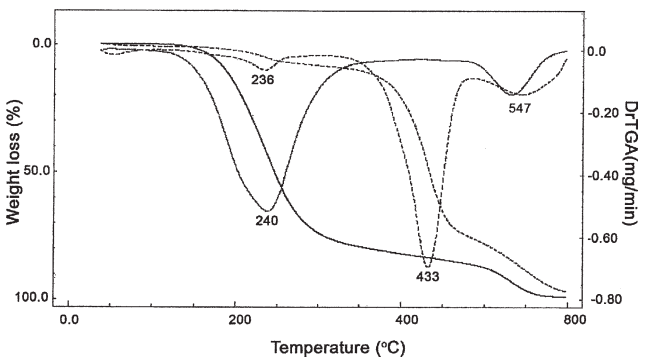


Figure 10 TGA and DrTGA thermograms for — NTM and for PNTM --------.

TABLE I
Thermogravimetric Analysis of NTM, PNTM, and their Complexes with Cu(II)

Polymer	Decomposition temperature (°C)				Residue (%)
NTM	240	534	–		0.0
PNTM	236	433	547		0.0
NTM-CuAc	245	366	557	745	17
NTM-$CuCl_2$	252	331	547	759	18
PNTM-$CuCl_2$	254	484	531	759	9
PNTM-CuAc	264	488		790	27

above 534°C is because of the complete decomposition of the polymer. The thermal decomposition temperature of the complexes as presented in Table I showing that initial weight loss of NTM-Cu at 245–252°C followed by two weight lost at 331–366°C and 547–557°C and final weight lost at 745–759°C. This result states that the two complexes are more stable than NTM. PNTM-Cu shows initial loss around 250–260. On increasing the temperature, further weight loss is observed above 480°C. The last step shows loss above 750°C. Additional loss was found in PNTM-$CuCl_2$ at 531°C. The weight loss of complexes above 750°C is because of the complete decomposition of the organic compounds. Thus, it concluded that the stability of two polymer complexes is higher than that of polymer PNTM. The weight loss retained is the percent of the metal uptake by the NTM and PNTM. This indicates that metal uptake is greatest in PNTM-CuAc (metal oxide residue 27%) and is lowest in PNTM-$CuCl_2$ (metal oxide residue 9%). Metal uptake by the NTM complexes approximately is the same, approximately more than 17%.

Biological activity

The monomer NTM, polymer PNTM, and their corresponding Cu(II) complexes were screened *in vitro* for their antibacterial activity against *E. coli, S. aureus, Pseudomonas* as well as for antifungal activity against *Candida albicans* using the agar well-diffusion method.[21–23] NTM, PNTM, and their complexes

TABLE II
***In Vitro* Bactericidal and Fungicidal Activity of Some Newly Synthesized Compounds**

Polymer	*S. aureus*	*E. coli*	*Pseudomonas*	*Candida albicans*
NTM	–	–	–	–
PNTM	+++	–	+++	–
PNTM-$CuCl_2$	++++	++	++++	+++
PNTM-CuAc	+	+	++++	–
NTM-$CuCl_2$	++	+	+++	–
NTM-CuAc	++++	++++	++++	–

+: 3–6 mm; ++: 6–9 mm; +++: 10–20 mm; ++++: > 20 mm.

individually exhibited varying degrees of inhibitory effects on the growth of the bacterial/fungal strains tested. These results, presented in Table II, show that that the synthesized ligands NTM, PNTM, and all Cu(II) complexes possess good biological activity. All compounds showed significant activity against *Pseudomonas* and insignificant activity against *E. coli* except NTM-CuAc, which has a significant activity against *E. coli*. These compounds generally showed significant to moderate antibacterial activity against *S. aureus.* However, only PNTM-CuAc showed good antifungal activity. It was evident from Table II that the activity of PNTM and their complexes, NTM complexes increased with coordination of the metal. Generally, chelation/coordinate reduces the polarity of the metal ion by partial sharing of its positive charge with donor groups and possibly π-electron delocalized within the whole chelate ring. This process, in turn, increases the lipophilic nature of the central metal atom, which favors its penetration through the lipoid layer of microorganism, killing them more effectively.[24–27]

CONCLUSIONS

NTM has been prepared and polymerized by a free radical mechanism. Monomer and its polymer characterized by IR and NMR, to prove their structure. NTA and its polymer PNTM found to have ability to form metal chelates with Cu(II) ion. Radical polymerization of monomer in the presence of copper salts (chloride and/or acetate) resulted the monomer-Cu complex (NTM-$CuCl_2$ and NTM-Ac) rather than polymer indicates that Cu(II) ion inhibited polymerization mechanism. Polymer complex (PNTM-$CuCl_2$ and PNTM-Ac) obtained by refluxing polymer in the presence of Cu-salt at 150°C. The structure of the complexes is inferred from data of IR, ESR, and EDX. It is found that the Cu(II) coordinated to ligands through the nitrogen of the thiazole ring and carbonyl oxygen. XRD and SEM suggest that the monomer complexes have a strongly crystalline structure compared with the polymer complexes, which shows that it is only weakly crystalline. The thermal analysis results show relatively good thermal stability of the Cu(II) complexes as compared by NTM and PNTM. The activity of the ligands and their complexes has been screened against *S. aureus, E. coli, Pseudomonas,* and *Candida albicans*. The results of these studies show the affinity as antibacterial and antifungal agents increased in most cases on complexation of NTM and PNTM with Cu(II) ion.

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